UNITED STATES PATENT AND TRADEMARK OFFICE

UNITED STATES DEPARTMENT OF COMMERCE
United States Patent and Trademark Office
Address: COMMISSIONER FOR PATENTS
P.O. Box 1450
Alexandria, Virginia 22313-1450
www.uspto.gov

APPLICATION NO.	FILING DATE	FIRST NAMED INVENTOR	ATTORNEY DOCKET NO.	CONFIRMATION NO.
09/807,354	11/21/2001	Peter B Dervan	025098/0603	6301

23620 7590 06/21/2004

FOLEY & LARDNER
402 WEST BROADWAY
23RD FLOOR
SAN DIEGO, CA 92101

EXAMINER	
KOSAR, ANDREW D	

ART UNIT	PAPER NUMBER
1654	

DATE MAILED: 06/21/2004

Please find below and/or attached an Office communication concerning this application or proceeding.

Office Action Summary	Application No.	Applicant(s)	
	09/807,354	DERVAN, PETER B	
	Examiner	Art Unit	
	Andrew D. Kosar	1654	

-- The MAILING DATE of this communication appears on the cover sheet with the correspondence address --

Period for Reply

A SHORTENED STATUTORY PERIOD FOR REPLY IS SET TO EXPIRE 3 MONTH(S) FROM THE MAILING DATE OF THIS COMMUNICATION.

- Extensions of time may be available under the provisions of 37 CFR 1.136(a). In no event, however, may a reply be timely filed after SIX (6) MONTHS from the mailing date of this communication.
- If the period for reply specified above is less than thirty (30) days, a reply within the statutory minimum of thirty (30) days will be considered timely.
- If NO period for reply is specified above, the maximum statutory period will apply and will expire SIX (6) MONTHS from the mailing date of this communication.
- Failure to reply within the set or extended period for reply will, by statute, cause the application to become ABANDONED (35 U.S.C. § 133). Any reply received by the Office later than three months after the mailing date of this communication, even if timely filed, may reduce any earned patent term adjustment. See 37 CFR 1.704(b).

Status

1)☐ Responsive to communication(s) filed on _____.

2a)☐ This action is **FINAL**. 2b)☒ This action is non-final.

3)☐ Since this application is in condition for allowance except for formal matters, prosecution as to the merits is closed in accordance with the practice under *Ex parte Quayle*, 1935 C.D. 11, 453 O.G. 213.

Disposition of Claims

4)☒ Claim(s) 26-41 is/are pending in the application.

4a) Of the above claim(s) _____ is/are withdrawn from consideration.

5)☐ Claim(s) _____ is/are allowed.

6)☒ Claim(s) 26-41 is/are rejected.

7)☐ Claim(s) _____ is/are objected to.

8)☐ Claim(s) _____ are subject to restriction and/or election requirement.

Application Papers

9)☒ The specification is objected to by the Examiner.

10)☒ The drawing(s) filed on 4/10/2001 is/are: a)☒ accepted or b)☐ objected to by the Examiner.

Applicant may not request that any objection to the drawing(s) be held in abeyance. See 37 CFR 1.85(a).

Replacement drawing sheet(s) including the correction is required if the drawing(s) is objected to. See 37 CFR 1.121(d).

11)☐ The oath or declaration is objected to by the Examiner. Note the attached Office Action or form PTO-152.

Priority under 35 U.S.C. § 119

12)☐ Acknowledgment is made of a claim for foreign priority under 35 U.S.C. § 119(a)-(d) or (f).

a)☐ All b)☐ Some * c)☐ None of:

1.☐ Certified copies of the priority documents have been received.

2.☐ Certified copies of the priority documents have been received in Application No. _____.

3.☐ Copies of the certified copies of the priority documents have been received in this National Stage application from the International Bureau (PCT Rule 17.2(a)).

* See the attached detailed Office action for a list of the certified copies not received.

Attachment(s)

1) ☒ Notice of References Cited (PTO-892)
2) ☐ Notice of Draftsperson's Patent Drawing Review (PTO-948)
3) ☐ Information Disclosure Statement(s) (PTO-1449 or PTO/SB/08) Paper No(s)/Mail Date _____.
4) ☐ Interview Summary (PTO-413) Paper No(s)/Mail Date. _____ .
5) ☐ Notice of Informal Patent Application (PTO-152)
6) ☐ Other: _____.

DETAILED ACTION

Claims 26-40 are pending in the current application. Claims 26-41[a] are rejected.

Priority

Applicant's claim of priority to U.S. provisional patent application 60/099,854, filed September 11, 1998, is acknowledged for the pending application (filed September 10, 1999 as PCT/US99/20489, which entered the national stage as U.S. application 09/807,354 on November 21, 2001).

Specification

The following guidelines illustrate the preferred layout for the specification of a utility application. These guidelines are suggested for the applicant's use.

Arrangement of the Specification

As provided in 37 CFR 1.77(b), the specification of a utility application should include the following sections in order. Each of the lettered items should appear in upper case, without underlining or bold type, as a section heading. If no text follows the section heading, the phrase "Not Applicable" should follow the section heading:

(a) TITLE OF THE INVENTION.
(b) CROSS-REFERENCE TO RELATED APPLICATIONS.
(c) STATEMENT REGARDING FEDERALLY SPONSORED RESEARCH OR DEVELOPMENT.
(d) INCORPORATION-BY-REFERENCE OF MATERIAL SUBMITTED ON A COMPACT DISC (See 37 CFR 1.52(e)(5) and MPEP 608.05. Computer program listings (37 CFR 1.96(c)), "Sequence Listings" (37 CFR 1.821(c)), and tables having more than 50 pages of text are permitted to be submitted on compact discs.) or

[a] Claims have been renumbered, as is proper, for examination purposes. See Claim Objections.

REFERENCE TO A "MICROFICHE APPENDIX" (See MPEP § 608.05(a). "Microfiche Appendices" were accepted by the Office until March 1, 2001.)

(e) BACKGROUND OF THE INVENTION.

(1) Field of the Invention.

(2) Description of Related Art including information disclosed under 37 CFR 1.97 and 1.98.

(f) BRIEF SUMMARY OF THE INVENTION.

(g) BRIEF DESCRIPTION OF THE SEVERAL VIEWS OF THE DRAWING(S).

(h) DETAILED DESCRIPTION OF THE INVENTION.

(i) CLAIM OR CLAIMS (commencing on a separate sheet).

(j) ABSTRACT OF THE DISCLOSURE (commencing on a separate sheet).

(k) SEQUENCE LISTING (See MPEP § 2424 and 37 CFR 1.821-1.825. A "Sequence Listing" is required on paper if the application discloses a nucleotide or amino acid sequence as defined in 37 CFR 1.821(a) and if the required "Sequence Listing" is not submitted as an electronic document on compact disc).

The disclosure is objected to because of the following informalities: The specification contains some typographical errors (See Page 32, line 24, for example). Appropriate correction is required.

Information Disclosure Statement

The listing of references in the specification is not a proper information disclosure statement. 37 CFR 1.98(b) requires a list of all patents, publications, or other information submitted for consideration by the Office, and MPEP § 609 A(1) states, "the list may not be incorporated into the specification but must be submitted in a separate paper." Therefore, unless the references have been cited by the examiner on form PTO-892, they have not been considered.

Claim Objections

The numbering of claims is not in accordance with 37 CFR 1.126 which requires the original numbering of the claims to be preserved throughout the prosecution. When claims are canceled, the remaining claims must not be renumbered. When new claims are presented, they must be numbered consecutively beginning with the number next following the highest numbered claims previously presented (whether entered or not). Claim 39 has been used twice in the claims set. Misnumbered claims 39-40 been renumbered 39-41,respectively, for the purpose of examination.

Claim 39 is objected to because it fails to further limit the claim upon which it depends. Claim 39 recites, "A method according to claim 38". The limitations of Claim 38 are inherent, as there are no further limitations.

Nonstatutory Double Patenting

The nonstatutory double patenting rejection is based on a judicially created doctrine grounded in public policy (a policy reflected in the statute) so as to prevent the unjustified or improper timewise extension of the "right to exclude" granted by a patent and to prevent possible harassment by multiple assignees. See *In re Goodman*, 11 F.3d 1046, 29 USPQ2d 2010 (Fed. Cir. 1993); *In re Longi*, 759 F.2d 887, 225 USPQ 645 (Fed. Cir. 1985); *In re Van Ornum*, 686 F.2d 937, 214 USPQ 761 (CCPA 1982); *In re Vogel*, 422 F.2d 438, 164 USPQ 619 (CCPA 1970);and, *In re Thorington,* 418 F.2d 528, 163 USPQ 644 (CCPA 1969).

A timely filed terminal disclaimer in compliance with 37 CFR 1.321(c) may be used to overcome an actual or provisional rejection based on a nonstatutory double patenting ground provided the conflicting application or patent is shown to be commonly owned with this application. See 37 CFR 1.130(b).

Effective January 1, 1994, a registered attorney or agent of record may sign a terminal disclaimer. A terminal disclaimer signed by the assignee must fully comply with 37 CFR 3.73(b).

Claims 26-28, 30, 32-36, and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1 and 5 of U.S. Patent No. 6,660,255 B1[b], herein '255. Claims 26-28, 30, 32-36, and 41 are anticipated by Claims 1 and 5 of '255 because Claims 1 and 5 teach:

A) A method of inhibiting the replication of a pathogen by administering a transcription inhibiting amount of at least one polyamide compound having the form $x_1x_2\ldots x_m$-γ-$x_{(m+1)}\ldots x_{(2m-1)}x2_m$-β-Dp", wherein $x_1, x_2, x_m, x_{(m+1)}, x_{(2m-1)}$ and $x2_m$ are carboxamide residues, γ is γ-aminobutyric acid or 2,4-diaminobutyric acid, β is β-alanine and Dp is diaminopropylamide, and m is an integer having a value from 3 to 6 ('255, Claim 1);

B) A method of inhibiting the replication of a pathogen by administering a transcription inhibiting amount of at least one polyamide, wherein the polyamide is chosen from a group consisting of ImPyPyPy-γ-ImPyPy-β-Dp, ImPy-β-ImPy-γ-ImPy-β-ImPy-β-Dp, ImPy-β-PyPyPyPy-β-ImPy-β-Dp, ImPy-β-ImPy-β-PyPyPyPy-β-ImPy-β-ImPy-β-Dp, ImPy-β-ImPyPyPy-β-ImPyPyPy-β-PyPy-β-Dp, ImImPyPy-γ-ImPyPyPy-β-Dp, and mixtures thereof wherein the Im is N-methylimidazole, Py is N-methylpyrrole, γ is γ-

[b] It is to be noted that U.S. Patent 6,660,255 B1 discloses in the specification that the preferred embodiment of 2,4-diaminobutyric acid is R-2,4-diaminobutyric acid.

aminobutyric acid, β is β-alanine, and Dp is dimethylaminopropylamide[c] ('255, Claim 5);

which fall entirely within the scope of Claims 26-28, 30, 32-36, and 41.

Claims 38 and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 1, 2, and 5 of '255. Claims 38 and 40 are anticipated by Claims 1, 2, and 5 of '255. The teaching of Claims 1 and 5 of '255 are discussed *supra*, and Claim 2 of '255 teaches that the pathogen is chosen from the group consisting of viruses, bacteria, fungi and protozoan. Claims 1, 2, and 5 of '255 fall entirely within the scope Claims 38 and 40. It is established *prima facie* that if one could inhibit gene transcription within an organism, such as bacteria, *supra*, one could practice the claimed invention of Claim 1 *in vitro*. Further, it is established *prima facie* that if one could inhibit replication of a pathogen, such as bacteria, by administering a transcription inhibiting amount of a polyamide, one would necessarily be contacting the polyamide with the gene inside the cell and would necessitate that the polyamide be cell permeable (Claims 38 and 40).

Claims 26-36, 38, 40 and 41 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 4 and 19 of U.S. Patent No. 6,301,312 B1[d], herein '312. Claims 26-36,

---

[c] It is to be noted that dimethylaminoproplyamide, or Dp, (in U.S. Patent 6,660,255 B1) and the terminal alkylamino group N,N-dimethylaminopropyl residue (in application 09/807,354) are structurally the same. The alkylamino group in the instant application would necessarily be bound to the polyamide through an amide linkage, and thus is Dp.

[d] It is to be noted that U.S. Patent 6,301,312 B1 discloses in the specification that the preferred embodiment of 2,4-diaminobutyric acid is R-2,4-diaminobutyric acid.

38, 40 and 41 are anticipated by Claims 4 and 19 of '312 because Claims 4 and 19 teach:

A) A method for inhibiting transcription of a gene in an organism, said method comprising:
Administering to said organism, one or more oligomers comprising N-heterocycles consisting of N-methyl pyrrole (*sic*) (Py) and N-methyl imidazole (*sic*) (Im), where the oligomers are selected to provide specific binding either singly or in pairs to a target dsDNA in a minor groove target site of said dsDNA,
werein, each of said oligomers comprises at least 6 of said heterocycles, where the pairing of heterocycles in relation to said target dsDNA is defined as Im/Py to G/C, Py/Im to C/G, and Py/Py to A/T and T/A and a pair of heterocycles refers to two heterocycles that are paired to a complementary pair of nucleotides in said dsDNA, and said heterocycles are linked by chains of 2 atoms, wherein at least some of the chains have NH, each oligomer comprising at least two units of consecutive heterocycles which form, at target sites, intramolecular pairs of heterocycles with another oligomer,
where when an oligomer forms intramolecular pairs, said oligomer comprises an internal molecule γ-aminobutyric acid, and
when two oligomers form intramolecular pairs, each oligomer comprises an internal β-alanine, said internal β-alanine is paired with an A or T;
where each oligomer terminates, at one or both termini, in a glycine, or β-alanine amino acid join ed to an alkyl chain of from 2 to 4 carbon atoms comprising a polar group, with the proviso that a γ-aminobutyric acid may join the termini to circularize an oligomer, where each oligomer has one or more hydrogen atoms away from the surface of said minor groove target site which may be substituted, wherein the total number of carbon atoms of substituents is not more than 30 carbon atoms,
wherein said target dsDNA is all or part of a target gene; and
said 1 to 2 oligomers bind to said target site, inhibiting transcription of said gene in said organism ('312, Claim 4);

B) A method according to claim 4, wherein said oligomer is polyamide ImPyPyPy-γ-ImPyPyPyPy-β-Dp, wherein γ is γ-aminobutyric, β is β-alanine, and Dp is diaminopropylamide ('312, Claim 19).

Claims 4 and 19 of '312 fall entirely within the scope of Claims 26-36, 38, 40 and 41.

Claims 38 and 40 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claims 4 and 19 of '312. Claims 38 and 40 are anticipated by Claims 4 and 19 of '312. The teaching of Claims 4 and 19 are discussed *supra*. Claims 4 and 19 of '312 fall entirely within the scope Claims 38 and 40. It is established *prima facie* that if one could inhibit gene transcription within an organism, *supra*, one could practice the claimed invention of Claim 1 *in vitro*. Further, it is established *prima facie* that if one could inhibit transcription in an organism through administration of a polyamide, one would necessarily be contacting the polyamide with the gene inside the cell and would necessitate that the polyamide be cell permeable (Claims 38 and 40).

Claims 29 and 31 are rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1of '255, in view of Claims 4 of '312, and further in view of Claim 1 of U.S. Patent 6,472,537 B1, herein '537.

The teachings of '255 and '312 are discussed *supra*. '255 does not specifically teach the use of 3-hydroxy-N-methylpyrrole ("Hp") as a carboxamide residue or the selection of carboxamide pair selection to correspond to DNA base pairs. Claim 4 of '312 does not teach the specific selection for Hp corresponding to a base pair. Claim 1 of '537 teaches:

> A) A polyamide comprising at least 3 consecutive carboxamide pairs that bind in a sequence specific manner to an equal number of consecutive DNA base pairs in a duplex DNA sequence, at least one of which consecutive DNA bas pairs is an AT or TA DNA base pair, wherein said polyamide comprises a 3-hydroxy-N-

> methylpyrrole ("Hp")/N-methylpyrrole ("Py") carboxamide pair to bind to each TA base pair in said consecutive DNA base pairs and a Py/Hp carboxamide pair to bind to each AT DNA base pair in said consecutive DNA base pairs;

Since '312 and '537 disclose all of the structural limitations of the claimed invention, such as Py/Im corresponding to a C/G base pair or Py/Py corresponding to an A/T base pair, for example, the invention as disclosed would necessarily possess the structural characteristics of corresponding to the claimed base pairs.

One of ordinary skill in the art would be motivated to combine the teachings *supra* to incorporate the pairings Hp/Py, Py/Hp, β/β into the polyamide structure to form better intermolecular pairings with base pairs of the target DNA, as discussed *supra*, with the anticipation that one could enhance the transcription blocking effect.

Further, the compounds glycine and 5-aminovaleric acid are obvious variants of β-alanine and γ-aminobutyric acid through carbon chain contraction and extension, respectively. One of ordinary skill in the art would be motivated to vary the carbon chain length to facilitate the specific alignment of the functional moieties, with the anticipation that one could enhance the transcription blocking effect.

Claim 37 is rejected under the judicially created doctrine of obviousness-type double patenting as being unpatentable over Claim 1of '255, in view of Claims 7 of '537.

The teachings of '255 are discussed *supra*. '255 does not teach the target sequence being in the promoter sequence. Claim 7 of '537 teaches that the target for the polyamide is a promoter sequence. One of ordinary skill in the art would be motivated to combine the teachings *supra* to target the promoter sequence, as it is the codon sequence at which transcription begins, with the expectation that inhibition at the promoter would prevent gene transcription from occurring.

Claim Rejections - 35 USC § 112

The following is a quotation of the second paragraph of 35 U.S.C. 112:

> The specification shall conclude with one or more claims particularly pointing out and distinctly claiming the subject matter which the applicant regards as his invention.

Claim 39 is rejected under 112, second paragraph, as being vague. Claim 39 recites, "A method according to Claim 38". The limitations of Claim 38 are met without further practice, and Claim 39 does not add limitations, and therefore does not limit the scope of the claimed invention.

Claims 26 and 30 are rejected under 35 U.S.C. 112, second paragraph, as being indefinite for failing to particularly point out and distinctly claim the subject matter which applicant regards as the invention.

Claim 26 lacks clear antecedent basis as it recites, in part, "... a nucleic acid sequence encoding a gene product operably linked to a promoter nucleic acid sequence...." The structure of the claim allows for two distinct interpretations. One interpretation is that the nucleic acid sequence (which

encodes a gene product) is operably linked to a promoter nucleic acid sequence. A second interpretation is that the gene product is operably linked to a promoter nucleic acid sequence.[e]

Claim 30 lacks clear antecedent basis as it recites, in part, "... said polyamide molecule comprises a first set of residues, each of which is independently a carboxamide residue or an aliphatic residue, and a second set or residues, each of which is independently a carboxamide residue or an aliphatic residue ...." The structure of the claim allows for two distinct interpretations. One interpretation is that the "each of which" refers back to the polyamide molecule. A second interpretation is that the "each of which" refers back to the first "set", or second "set", of residues – as a collection of residues.[f]

The following is a quotation of the first paragraph of 35 U.S.C. 112:

> The specification shall contain a written description of the invention, and of the manner and process of making and using it, in such full, clear, concise, and exact terms as to enable any person skilled in the art to which it pertains, or with which it is most nearly connected, to make and use the same and shall set forth the best mode contemplated by the inventor of carrying out his invention.

Claims 26-41 are rejected under 35 U.S.C. 112, first paragraph, because the specification, while being enabling for *in vitro* inhibition of gene transcription, does not reasonably provide enablement for *in vivo* gene transcription. The specification does not enable any person skilled in the art to which it pertains, or

---

[e] Examination on the merits has proceeded by the Examiner's interpretation to mean, "nucleic acid operably linked to a promoter nucleic acid.

[f] Examination on the merits has proceeded by the Examiner's interpretation where the residues are part of the first, or second "set" of residues.

with which it is most nearly connected, to use the invention commensurate in scope with these claims.

The factors to be considered in determining whether a disclosure meets the enablement requirements of 35 U.S.C. 112, first paragraph, have been described in *In re Wands*, 858 F.2d 731, 8 USPQ2d 1400 (Fed. Cir., 1988). The court in Wands states, "Enablement is not precluded by the necessity for some experimentation, such as routine screening. However, experimentation needed to practice the invention must not be undue experimentation. The key word is 'undue', not 'experimentation'" (Wands, 8 USPQ2sd 1404). Clearly, enablement of a claimed invention cannot be predicated on the basis of quantity of experimentation required to make or use the invention. "Whether undue experimentation is needed is not a single, simple factual determination, but rather is a conclusion reached by weighing many factual considerations" (Wands, 8 USPQ2d 1404). Among these factors are: (1) the nature of the invention; (2) the state of the prior art; (3) the relative skill of those in the art; (4) the predictability or unpredictability of the art; (5) the breadth of the claims; (6) the amount of direction or guidance presented; (7) the presence or absence of working examples; and (8) the quantity of experimentation necessary.

While all of these factors are considered, a sufficient amount for a *prima facie* case is discussed below.

(1) The nature of the invention:

The claims are directed to a method of inhibiting transcription in a gene by a polyamide compound.

(2) The state of the prior art:

The use of bulky and sterically hindering groups as inhibitors is uncertain. Grunewald shows that inhibitors, which were conformationally-restricted and having PNMT-inhibitory activity, were dependent upon the τ_2-angle and the amount of steric bulk (Grunewald, et al., *J. Med. Chem.* 1996, Vol 39, No 18, Page 3543). Additionally, similar compounds, when tested against the α_2-adrenoreceptor, were found to be regulated mainly by steric bulk, and when modified caused deleterious effects to ligand:receptor binding (Grunewald, *ibid.*).

The structure of DNA in the current state of the art remains largely unknown. One could not predict what type of helix a DNA structure will take, that is the A, B, or Z form. Because of this, one would not be able to predict the pitch or diameter, for example, that would be present in the DNA sequence. Further, the major and/or minor groove are affected by environmental conditions, such as levels of hydration and/or salt concentrations that are present (see page 4 http://www.Tulane.edu/~biochem/Nolan/lectures/rna/DNAstruct2001.htm).

The state of the art in genome sequence anaylsis is still unperfected. Mitchell and Bell state that in an effort to find a calpain gene in the *Plasmodium falciparum* genome, they found that, "[m]ultiple errors were found in the annotation {of the genome}[9] including an anomalous start (AAA,CAC,GTA,TAG) and termination codons (AAT,ATA,AAG, CTT, GAA,GGG,TTC, TTT)...and the absence of a number of experimentally known genes. (D Mitchell and A Bell, Malaria Journal, page 2, column 2).

---

[9] Inserted by Examiner to clarify the statement.

(3) The relative skill of those in the art:

The relative skill of those in the art is high.

(4) The predictability or unpredictability of the art:

Since the state of DNA structure prediction and accurate genome sequence information is not currently known and the ability to predict how a ligand will interact with a receptor remains largely unsolved, means for providing a ligand, in the instant application – a polyamide, that will successfully bind to a receptor, in the instant application – a DNA sequence (gene), when the structure of the DNA (type, pitch, and groove dimensions, for example) is dependent on the sequence, and the state of the art in sequence identification is currently imperfect, inhibition of any gene transcription with polyamides is highly unpredictable.

(5) The breadth of the claims:

The claims are drawn to a method of inhibiting transcription of a gene. Thus, the claims taken together with the specification imply inhibition of the transcription of any gene.

(6) The amount of direction or guidance presented and (7) The presence or absence of working examples:

The specification has provided teachings on how to select the ligand (polyamide), if the receptor (DNA) sequence was known. However, the specification does not provide adequate guidance of which gene(s) one would be able to inhibit from the plurality of genes that the claimed invention encompasses, nor does it provide adequate guidance on the limitations of the

known DNA sequences. Further, the claims and specification do not provide for selection of the ligand in view of the sterics of the ligand and the impact it would have on its ability to inhibit gene transcription.

The polyamide ligand comprises substituted imidazole and pyrrole moieties which are bulky and can contribute to steric bulk, which would contribute to an inability to inhibit transcription. The state of the art is such that the target DNA (gene) structure is dynamic and unpredictable, with regard to the shape (type, pitch, and groove, for example), and the current state of the art in regards to gene sequencing is still highly unpredictable, and as such, one of skill in the art could not adequately predict that if they were to select the appropriate ligand, using the appropriate base pair selection rules, that they would be able to inhibit gene transcription.

There is a lack of working examples for *in vivo* inhibition of a gene. Lipinski's rule of fives states that poor absorption or permeation of a drug, in the instant application a polyamide, is more likely when any of the following conditions are met: the molecular weight (MW) of the drug is over 500; the LogP is over 5 (or MLogP is over 4.15); the compound (polyamide) has more than 5 H-bond donors (expressed as the sum of OHs and NHs); or the compound (polyamide) has more than 10 H-bond acceptors (expressed as the sum of Ns and Os), where the exception to the rules is compounds that would be substrates for biological transporters (Lipinski, *et al.*, Advanced Drug Delivery Reviews, 1997, 23, page 9, first column). Because of the breadth of the claims, embodiments of the instant application would exceed the limitations of the

molecular weight requirement, thus minimizing absorption and/or permeation of the drug, and as a consequence, the drug would be less likely to inhibit gene transcription *in vivo*. Further, the smallest embodiment consisting of 6 pyrroles, 2 glycines and a single carbon chain terminal amine results in a molecular weight over 500. As predicted by the violation of the first of Lipinski's rules, it would be expected that the polyamide would be characterized by poor permeation.

(8) The quantity of experimentation necessary:

Because the claims are drawn to inhibition of any gene, the specification does not provide sufficient guidance to overcome the limitations of the current state of the art, as discussed *supra*, and the high unpredictability and the lack of guidance provided in the specification, one of skill in the art would be burdened with undue experimentation to practice the invention as claimed.

It is the examiner's position that one skilled in the art could not practice the invention commensurate in the scope of the claims without undue experimentation.

Accordingly, the Examiner has determined that while Applicant is enabled for *in vitro* inhibition of gene transcription in gel mobility shift assays, with the polyamide embodiments of the claims, and *in vitro* inhibition of transcription driven by the HER2/neu promoter sequence *in vitro*, with the polyamide embodiments of the claims, Applicant is not enabled for *in vivo* gene inhibition with the polyamide embodiments of the claims.

Claim Rejections - 35 USC § 102

> (e) the invention was described in a patent granted on an application for patent by another filed in the United States before the invention thereof by the applicant for patent, or on an international application by another who has fulfilled the requirements of paragraphs (1), (2), and (4) of section 371(c) of this title before the invention thereof by the applicant for patent.

The changes made to 35 U.S.C. 102(e) by the American Inventors Protection Act of 1999 (AIPA) and the Intellectual Property and High Technology Technical Amendments Act of 2002 do not apply when the reference is a U.S. patent resulting directly or indirectly from an international application filed before November 29, 2000. Therefore, the prior art date of the reference is determined under 35 U.S.C. 102(e) prior to the amendment by the AIPA (pre-AIPA 35 U.S.C. 102(e)).

Claims 26-28, 30, 32-36, and 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Claims 1 and 5 of U.S. Patent No. 6,660,255 B1.

Claims 1 and 5 of U.S. Patent 6,660,255 B1 teach:

A) A method of inhibiting the replication of a pathogen by administering a transcription inhibiting amount of at least one polyamide compound having the form $x_1x_2\ldots x_m$-γ-$x_{(m+1)}\ldots x_{(2m-1)}x2_m$-β-Dp", wherein x_1,x_2,x_m,$x_{(m+1)}$,$x_{(2m-1)}$ and $x2_m$ are carboxamide residues, γ is γ-aminobutyric acid or 2,4-diaminobutyric acid, β is β-alanine and Dp is diaminopropylamide, and m is an integer having a value from 3 to 6 ('255, Claim 1);

B) A method of inhibiting the replication of a pathogen by administering a transcription inhibiting amount of at least one polyamide, wherein the polyamide is chosen from a group

consisting of ImPyPyPy-γ-ImPyPy-β-Dp, ImPy-β-ImPy-γ-ImPy-β-ImPy-β-Dp, ImPy-β-PyPyPyPy-β-ImPy-β-Dp, ImPy-β-ImPy-β-PyPyPyPy-β-ImPy-β-ImPy-β-Dp, ImPy-β-ImPyPyPy-β-ImPyPyPy-β-PyPy-β-Dp, ImImPyPy-γ-ImPyPyPy-β-Dp, and mixtures thereof wherein the Im is N-methylimidazole, Py is N-methylpyrrole, γ is γ-aminobutyric acid, β is β-alanine, and Dp is dimethylaminopropylamide[h] ('255, Claim 5);

which fall entirely within the scope of Claims 26-28, 30, 32-36, and 41.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 26-36, 38, 40 and 41 are rejected under 35 U.S.C. 102(e) as being anticipated by Claims 4 and 19 of U.S. Patent No. 6,301,312 B1.

Claims 4 and 19 of U.S. Patent 6,301,312 B1 teach:

A) A method for inhibiting transcription of a gene in an organism, said method comprising:
Administering to said organism, one or more oligomers comprising N-heterocycles consisting of N-methyl pyrrole (*sic*) (Py) and N-methyl imidazole (*sic*) (Im), where the oligomers are selected to

[h] It is to be noted that dimethylaminoproplyamide, or Dp, (in U.S. Patent 6,660,255 B1) and the terminal alkylamino group N,N-dimethylaminopropyl residue (in application 09/807,354) are structurally the same. The alkylamino group in the instant application would necessarily be bound to the polyamide through an amide linkage, and thus is Dp.

provide specific binding either singly or in pairs to a target dsDNA in a minor groove target site of said dsDNA,
werein, each of said oligomers comprises at least 6 of said heterocycles, where the pairing of heterocycles in relation to said target dsDNA is defined as Im/Py to G/C, Py/Im to C/G, and Py/Py to A/T and T/A and a pair of heterocycles refers to two heterocycles that are paired to a complementary pair of nucleotides in said dsDNA, and said heterocycles are linked by chains of 2 atoms, wherein at least some of the chains have NH, each oligomer comprising at least two units of consecutive heterocycles which form, at target sites, intramolecular pairs of heterocycles with another oligomer,
where when an oligomer forms intramolecular pairs, said oligomer comprises an internal molecule γ-aminobutyric acid, and
when two oligomers form intramolecular pairs, each oligomer comprises an internal β-alanine, said internal β-alanine is paired with an A or T;
where each oligomer terminates, at one or both termini, in a glycine, or β-alanine amino acid join ed to an alkyl chain of from 2 to 4 carbon atoms comprising a polar group, with the proviso that a γ-aminobutyric acid may join the termini to circularize an oligomer, where each oligomer has one or more hydrogen atoms away from the surface of said minor groove target site which may be substituted, wherein the total number of carbon atoms of substituents is not more than 30 carbon atoms,
wherein said target dsDNA is all or part of a target gene; and
said 1 to 2 oligomers bind to said target site, inhibiting transcription of said gene in said organism ('312, Claim 4);

B) A method according to claim 4, wherein said oligomer is polyamide ImPyPyPy-γ-ImPyPyPy-β-Dp, wherein γ is γ-aminobutyric, β is β-alanine, and Dp is diaminopropylamide ('312, Claim 19).

Claims 4 and 19 of '312 fall entirely within the scope of Claims 26-36, 38, 40 and 41.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application

and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claims 38 and 40 are rejected under 35 U.S.C. 102(e) as being anticipated by Claims 4 and 19 of U.S. Patent No. 6,301,312 B1. Additionally, Claims 38 and 40 are rejected under 35 U.S.C. 102(e) as being anticipated by Claims 1, 2, and 5 of U.S. Patent No. 6,660,255 B1. The teaching of Claims 1 and 5 of '255 are discussed *supra*, and Claim 2 of '255 teaches that the pathogen is chosen from the group consisting of viruses, bacteria, fungi and protozoan. Claims 1, 2, and 5 of '255 fall entirely within the scope Claims 38 and 40. It is established *prima facie* that if one could inhibit gene transcription within an organism, such as bacteria, *supra*, one could practice the claimed invention of Claim 1 *in vitro*. Further, it is established *prima facie* that if one could inhibit replication of a pathogen, such as bacteria, by administering a transcription inhibiting amount of a polyamide, one would necessarily be contacting the polyamide with the gene inside the cell and would necessitate that the polyamide be cell permeable (Claims 38 and 40).

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 102(e) might be overcome either by a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not the invention "by another," or by an appropriate showing under 37 CFR 1.131.

Claim Rejections - 35 USC § 103

The following is a quotation of 35 U.S.C. 103(a) which forms the basis for all obviousness rejections set forth in this Office action:

> (a) A patent may not be obtained though the invention is not identically disclosed or described as set forth in section 102 of this title, if the differences between the subject matter sought to be patented and the prior art are such that the subject matter as a whole would have been obvious at the time the invention was made to a person having ordinary skill in the art to which said subject matter pertains. Patentability shall not be negatived by the manner in which the invention was made.

Claims 29 and 31 are rejected under 35 U.S.C. 103(a) as being obvious over Claims 1 of U.S. Patent 6,660,255 B1, in view of Claims 4 of U.S. Patent 6,301,312, in further view of Claim 1 of U.S. Patent 6,472,537 B1.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject

matter of the reference and the claimed invention were, at the time the invention was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The teachings of '255 and '312 are discussed *supra*. '255 does not specifically teach the use of 3-hydroxy-N-methylpyrrole ("Hp") as a carboxamide residue or the selection of carboxamide pair selection to correspond to DNA base pairs. Claim 4 of '312 does not teach the specific selection for Hp corresponding to a base pair. Claim 1 of '537 teaches:

> A) A polyamide comprising at least 3 consecutive carboxamide pairs that bind in a sequence specific manner to an equal number of consecutive DNA base pairs in a duplex DNA sequence, at least one of which consecutive DNA bas pairs is an AT or TA DNA base pair, wherein said polyamide comprises a 3-hydroxy-N-methylpyrrole ("Hp")/N-methylpyrrole ("Py") carboxamide pair to bind to each TA base pair in said consecutive DNA base pairs and a Py/Hp carboxamide pair to bind to each AT DNA base pair in said consecutive DNA base pairs;

Since '312 and '537 disclose all of the structural limitations of the claimed invention, such as Py/Im corresponding to a C/G base pair or Py/Py corresponding to an A/T base pair, for example, the invention as disclosed would necessarily possess the structural characteristics of corresponding to the claimed base pairs.

One of ordinary skill in the art would be motivated to combine the teachings *supra* to incorporate the pairings Hp/Py, Py/Hp, β/β into the polyamide structure to form better intermolecular pairings with base pairs of the target DNA, as discussed *supra*, with the anticipation that one could enhance the transcription blocking effect.

Further, the compounds glycine and 5-aminovaleric acid are obvious variants of β-alanine and γ-aminobutyric acid through carbon chain contraction and extension, respectively. One of ordinary skill in the art would be motivated to vary the carbon chain length to facilitate the specific alignment of the functional moieties, with the anticipation that one could enhance the transcription blocking effect.

Claim 37 is rejected under 35 U.S.C. 103(a) as being obvious over Claims 1 of U.S. Patent 6,660,255 B1, in view of Claim 7 of U.S. Patent 6,472,537 B1.

The applied reference has a common inventor with the instant application. Based upon the earlier effective U.S. filing date of the reference, it constitutes prior art only under 35 U.S.C. 102(e). This rejection under 35 U.S.C. 103(a) might be overcome by: (1) a showing under 37 CFR 1.132 that any invention disclosed but not claimed in the reference was derived from the inventor of this application and is thus not an invention "by another"; (2) a showing of a date of invention for the claimed subject matter of the application which corresponds to subject matter disclosed but not claimed in the reference, prior to the effective U.S. filing date of the reference under 37 CFR 1.131; or (3) an oath or declaration under 37 CFR 1.130 stating that the application and reference are currently owned by the same party and that the inventor named in the application is the prior inventor under 35 U.S.C. 104, together with a terminal disclaimer in accordance with 37 CFR 1.321(c). For applications filed on or after November 29, 1999, this rejection might also be overcome by showing that the subject matter of the reference and the claimed invention were, at the time the invention

was made, owned by the same person or subject to an obligation of assignment to the same person. See MPEP § 706.02(l)(1) and § 706.02(l)(2).

The teachings of '255 are discussed *supra*. '255 does not teach the target sequence being in the promoter sequence. Claim 7 of '537 teaches that the target for the polyamide is a promoter sequence. One of ordinary skill in the art would be motivated to combine the teachings *supra* to target the promoter sequence, as it is the codon sequence at which transcription begins, with the expectation that inhibition at the promoter would prevent gene transcription from occurring.

Any inquiry concerning this communication or earlier communications from the examiner should be directed to Andrew D. Kosar whose telephone number is (571)272-0913. The examiner can normally be reached on Monday - Friday 8am-430pm.

If attempts to reach the examiner by telephone are unsuccessful, the examiner's supervisor, Brenda Brumback can be reached on (571)272-0961. The fax phone number for the organization where this application or proceeding is assigned is 703-872-9306.

Information regarding the status of an application may be obtained from the Patent Application Information Retrieval (PAIR) system. Status information for published applications may be obtained from either Private PAIR or Public PAIR. Status information for unpublished applications is available through Private PAIR only. For more information about the PAIR system, see http://pair-direct.uspto.gov. Should you have questions on access to the Private PAIR system, contact the Electronic Business Center (EBC) at 866-217-9197 (toll-free).

Patricia Leith
Primary Examiner
Art Unit 1654

Andrew D. Kosar, Ph.D.
June 14, 2004

PATRICIA LEITH
PRIMARY EXAMINER

BRUCE KISLIUK, DIRECTOR
TECHNOLOGY CENTER 1600